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10/670,915	09/24/2003	Richard Daifuku	021227-000310US	6525

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EXAMINER	
OLSON, ERIC	
ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/670,915	DAIFUKU ET AL.	
	Examiner	Art Unit	
	ERIC S. OLSON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8-15 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 8-15* is/are rejected.

7)☒ Claim(s) *29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/23/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted March 23, 2009 wherein claim 1 is amended and new claim 29 is introduced. This application claims benefit of provisional application 60/413337, filed September 24, 2002.

Claims 1, 8-15, and 29 are pending in this application.

Claims 1, 8-15, and 29 as amended are examined on the merits herein.

Applicant's amendment, submitted March 23, 2009, with respect to the rejection of instant claim 1 under 35 USC 102(b) for being anticipated by Sculnick et al., has been fully considered and found to be persuasive to remove the rejection as the claim has been amended to add the additional proviso that when R^9 and R^{10} are both other than acyl, R^6 is a phosphate species $OP(O)(OR^{14})(OR^{14})$. Therefore the rejection is withdrawn.

Applicant's amendment necessitates the following new grounds of rejection:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim recites the limitation that R^6 is OR^{14}, wherein R^{14} is selected from H, substituted or unsubstituted alkyl, and $P(O)(OR^{17})(OR^{17})$, wherein R^{17}

is substituted alkyl, substituted or unsubstituted alkyloxy, or substituted or unsubstituted phenyl. However, claim 1 has been amended to recite the additional limitation that When R^9 and R^{10} are both other than acyl, R^6 is $OP(O)(OR^{14})(OR^{14})$. Because R^{14} and R^{17} are not coextensive in scope, it is unclear whether this proviso expands the scope of the groups R^6 to all groups $OP(O)(OR^{14})(OR^{14})$, or whether it merely limits the scope to all groups $OP(O)(OR^{14})(OR^{14})$ wherein the group R^{14} is also a group falling within R^{17}. Therefore the claim is indefinite. Because Applicant's amendment necessitated this new ground of rejection, the rejection is made **FINAL**.

Claim Rejections - 35 USC § 103

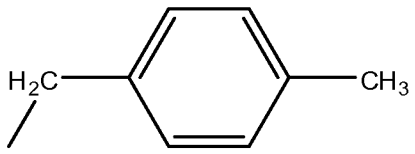
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Skulnick. (US patent 4171431, of record in previous action)

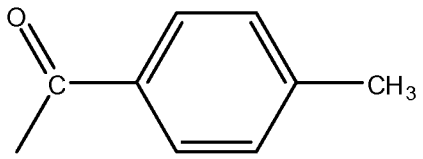
Skulnick discloses antiviral 5,6-dihydro-triazine deoxynucleosides having a structure including the structure of instant claim 1. (column 2 lines 20-69, the embodiment wherein Y=H or phosphono, Y' = H, X = NH, N-alkyl, or N-acetyl, Z = O, R = H or C2-C4 alkyl, and R' = H) These compounds are active *in vivo* against susceptible DNA viruses. (column 4 lines 52-63) Furthermore Skulnick discloses various 1-(2-deoxy-β-D-ribofuranosyl)-4-imino-3,4,5,6-tetrahydro-s-triazine-2-(1H)-ones (column 27

lines 9-20) having an H or alkyl group at the 5- position. Because Skulnick also discloses that these compounds exist as multiple tautomeric forms (column 2 lines 14-19) the disclosure therefore also includes various 1-(2-deoxy-β-D-ribofuranosyl)-4-amino-5,6-dihydro-s-triazine-2-(1H)-ones as tautomers. Said compounds differ from the claimed compounds merely by the single substitution of a phosphono group at position Y or an N-acyl group at position X. Furthermore other compounds disclosed in column 25 lines 43-58 of Skulnick are 1-(2-deoxy-3,5-di-O-toluoyl-β-D-ribofuranosyl)-4-acetylimino-3,4,5,6-tetrahydro-s-triazine-2-(1H)-ones (column 27 lines 9-20) having an H or alkyl group at the 5- position. These differ from the claimed compound merely by the removal of the 3'- Toluoyl group to unmask the 3' OH group of the ribose moiety. Note that the 5'-O-toluoyl is reasonably considered to be a "substituted alkyl group" according to the definition of substituent given on p. 8 lines 1-14 and p. 10 lines 15-34 of the specification as originally filed. Specifically, "alkyl" as used in the instant specification indicates either a saturated or unsaturated, straight-chain, or cyclic hydrocarbon. Therefore the group:



p-methylbenzyl

Is an alkyl group according to the instant specification, especially in view of the recitation on p. 8 of various unsaturated and cyclic groups that are considered to be "alkyl groups." Furthermore since p. 10 of the specification defines a substituent as including the oxo (=O) group, and p. 8 lines 24-27 of the specification discuss acyl groups as a derivative of alkyl groups, the group toluoyl:



Toluoyl

Is considered to be a substituted alkyl group according to the claims, and fulfills the requirements of claim 1, position R^{14} when R^9 or R^{10} is acyl as is the case for the compound 1-(2-deoxy-3,5-di-O-toluoyl-β-D-ribofuranosyl)-4-acylimino-3,4,5,6-tetrahydro-s-triazine-2-(1H)-one. 5'- phosphates are mentioned in column 5 lines 9-10 as being useful for the same purpose as the free nucleosides, and column 11 lines 1-6 discloses methods for phosphorylating the 5'- position of the nucleoside.

Skulnick does not specifically disclose the exact compounds recited in instant claim 1.

It would have been obvious to one of ordinary skill in the art at the time of the invention to make the compounds recited in instant claim 1. One of ordinary skill in the art would have been motivated to make them because they are included within the limitations of the broad recitation of Skulnick, and are furthermore very structurally similar to several compounds explicitly disclosed by Skulnick in figure 1 below:

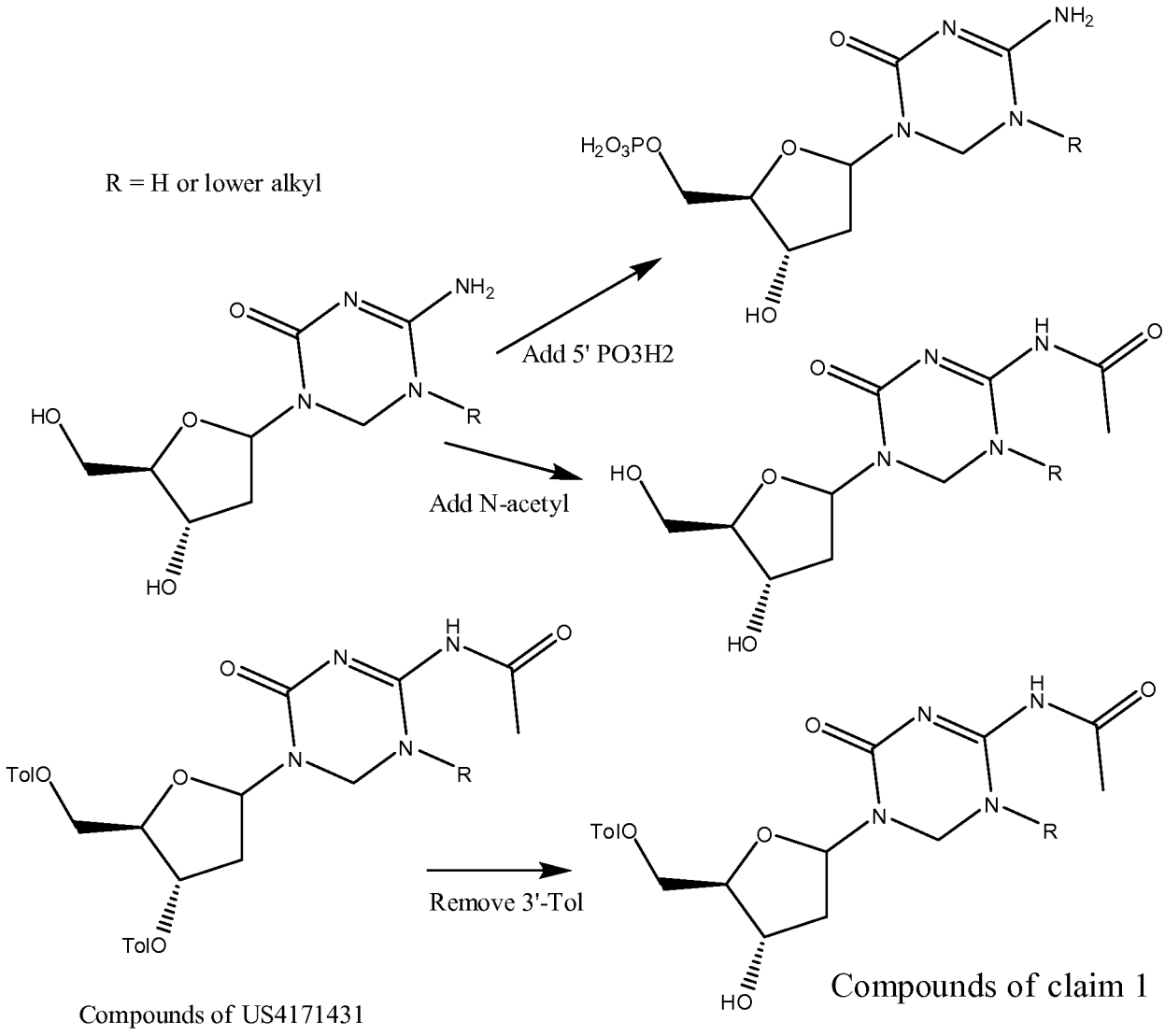


Fig. 1 - Substitutions necessary to arrive at the claimed invention

One of ordinary skill in the art would reasonably have expected success because all of these compounds fall within the general teaching of Skulnick. Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted March 23, 2009, with respect to the rejection of claim 1 under 35 USC 102(b) are moot as the rejection has

been withdrawn. Applicant's arguments made in anticipation of a rejection under 35 USC 103(a) are addressed below:

Applicant argues that there is no motivation to pick the particular claimed compounds out of the broad genus taught by Skulnick. However, the recitation of certain specific structures by Skulnick, as illustrated in Figure 1, directs one of ordinary skill in the art to compounds similar to those structures. Although the broad genus of Skulnick discloses thousands of compounds, arriving at the compounds of claim 1 from the specific examples of Skulnick only requires a single substitution, thereby drastically narrowing the scope of compounds among which one of ordinary skill in the art would choose. Applicant further argues that the fact that Skulnick discloses 2-oxo-4-amino compounds having no N-acyl or 5'- phosphate group means that there is no motivation to select the claimed compounds. However, column 25 of Skulnick, as discussed above, does exemplify compounds having an N-acetyl group. Furthermore, according to MPEP 2123, disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. See In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." See In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) 27 F.3d at 554, 31 USPQ2d at 1132.). 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). The mere fact that a number of 4-amino compounds are recited does not constitute a teaching away from 4-acylamino compounds.

Applicant further argues that there is no teaching that would lead one of ordinary skill in the art to modify the claimed compounds with an N-acyl or 5'- phosphate group. However, the disclosure of Skulnick does discuss phosphate groups in column 5 lines 9-10 as discussed above, and exemplifies a number of acyl-imino compounds in claim 25 that are tautomers of acylamino compounds. Therefore Skulnick does particularly point out these chemical groups as worthy of attention.

Finally, Applicant argues that the art is unpredictable. While this may be the case if one is blindly selecting a compound from the entirety of the broad genus, it is not the case if the prior art gives specific examples that are very close in structure to the claims. Making the single substitutions described in the body of the rejection is predictable as the chemical transformations involved are simple. This is especially true given the teaching of column 10 lines 59-61 which discloses a method of making 5'-monoesters, and column 11 lines 1-6, which discloses methods for phosphorylating the 5'- position of the nucleoside.

For these reasons the rejection is deemed proper. Because Applicant's amendment necessitated this new ground of rejection, the rejection is made **FINAL**.

The following rejections of record in the previous action are maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skulnick (Reference cited in PTO-1449) as applied to claim 1 above, and further in view of Cullis et al. (US patent 6852334, of record in previous action) the disclosure of Skulnick is discussed above. Skulnick does not disclose a composition further comprising an amphiphilic species and a dendrimeric polyamine according to instant claims 12-15.

Cullis et al. discloses conjugates that can be incorporated into stabilized plasma lipid particles comprising a lipid anchor, a non-immunogenic polypeptide, and a polycationic moiety, and further comprising a bioactive agent and a second lipid. (column 2 line 33 – column 3 line 23) The polycationic moiety can have between 2-15 positive charges, derived from basic amino acids or amines, for example tetralysine, as well as polycationic dendrimers. (column 13 lines 17-32) These polycations thus include compounds reasonably considered to be polyamines, and one of ordinary skill in the art would recognize polyamine dendrimers as being another useful embodiment of this species. These conjugates are incorporated into lipid-based drug formulations such as liposomes, composed of specific lipids such as phospholipids which are considered to be composed of a hydrophobic domain and a hydrophilic domain covalently bound to one another. (column 16, lines 11-34) These liposome formulations are useful for delivering bioactive agents such as antineoplastic agents and nucleoside analogs. (column 21 lines 29-60) The formulations are preferably delivered as an aqueous intravenous solution. (column 24 lines 52-60)

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the dihydro-azacytidine compounds of Skulnick in a formulation containing the liposomes and conjugates of Cullis et al. One of ordinary skill in the art would have been motivated to deliver the drugs in this manner because Cullis et al. discloses a method for delivering nucleoside analogs, which would be recognized by one of ordinary skill in the art as including the dihydro-5-azacytidine analogs of Skulnick. One of ordinary skill in the art would reasonably have expected success because formulating a specific known drug in a specific known drug delivery formulation is well within the ordinary and routine level of skill in the art.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted March 23, 2009, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant's arguments are the same as those made with respect to the rejection over Skulnick et al. above and are not found persuasive for the same reasons. Therefore the rejection is maintained and made **FINAL**.

Claims 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skulnick (Reference cited in PTO-1449) as applied to claim 1 above, and further in view of McGuigan et al. (Reference U of record in previous action) the disclosure of Skulnick is discussed above. Skulnick does not disclose a compound wherein R^6 is as recited in claims 10 and 11.

McGuigan et al. discloses bis(2,2,2-trichloroethyl) phosphate derivatives of AZT showing enhanced membrane penetration and being able to be hydrolyzed to the active phosphate *in vivo*. (p. 355, right column, first paragraph, p. 356 figure 1) These compounds exert an anti-HIV effect by being cleaved intracellularly and trapped inside of the target cell. (p. 357, right column, last paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the compounds of Skulnick with a bis(2,2,2-trichloroethyl) phosphate group as disclosed by McGuigan et al. One of ordinary skill in the art would have been motivated to make this substitution because McGuigan et al. discloses that the bis(2,2,2-trichloroethyl) phosphate group is a prodrug that releases nucleosides intracellularly, and Skulnick already discloses phosphorylated nucleosides. One of ordinary skill in the art would reasonably have expected success because McGuigan et al. already discloses that this approach works when applied to AZT, a deoxynucleoside analog of similar structure.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted March 23, 2009, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant's arguments are the same as those made with respect to the rejection over Skulnick et al. above and are not found persuasive for the same reasons.

Applicant further argues that the compound (AZT) that is modified in the teaching of McGuigan et al. is sufficiently different from the compounds of the instant invention

that one of ordinary skill in the art would not have been able to apply the teachings of McGuigan et al. to the compounds of Skulnick. However, McGuigan et al. discloses that the need for metabolic activation by phosphorylation is common to nucleoside analogs in general (column 355 left column last paragraph) and that nucleoside phosphates suffer from poor membrane penetration. Both of these teachings would be seen by one of ordinary skill in the art to apply to nucleoside analogs in general and not merely to AZT and closely related compounds. This is especially true given that Skulnick already teaches 5'- phosphate compounds that would clearly be expected to suffer from the same problems with membrane permeability. Furthermore given that these phosphates would be expected to suffer from poor membrane permeability, one of ordinary skill in the art would expect that the modifications described by McGuigan et al. would improve their membrane permeability and thus improve their activity. This effect would be expected to apply to both AZT phosphate and the phosphates of Skulnick because it relies on changes in the physical characteristics (charge and lipophilicity) of the compounds, which are relatively predictable.

Therefore the rejection is maintained and made **FINAL**.

Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skulnick (Reference cited in PTO-1449) as applied to claim 1 above, and further in view of McGuigan et al. 2 (Reference V of record in previous action) the disclosure of Skulnick is discussed above. Skulnick does not disclose a compound wherein R^6 is as recited in claims 10 and 11.

McGuigan et al. 2 discloses an aryl (2,2,2-trichloroethyl) phosphate derivative of AZT showing enhanced membrane penetration and being able to be hydrolyzed to the active phosphate *in vivo*. (p. 312, first and second paragraphs and figure 1, p. 313 first paragraph) These compounds exert an anti-HIV effect by being cleaved intracellularly and trapped inside of the target cell. (p. 317, last paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the compounds of Skulnick with an aryl (2,2,2-trichloroethyl) phosphate group as disclosed by McGuigan et al. 2. One of ordinary skill in the art would have been motivated to make this substitution because McGuigan et al. 2 discloses that the an aryl (2,2,2-trichloroethyl) phosphate group is a prodrug that releases nucleosides intracellularly, and Skulnick already discloses phosphorylated nucleosides. One of ordinary skill in the art would reasonably have expected success because McGuigan et al. 2 already discloses that this approach works when applied to AZT, a deoxynucleoside analog of similar structure.

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted March 23, 2009, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant's arguments are the same as those made with respect to the rejection over Skulnick et al. above and are not found persuasive for the same reasons.

Applicant further argues that the compound (AZT) that is modified in the teaching of McGuigan et al. 2 is sufficiently different from the compounds of the instant invention

that one of ordinary skill in the art would not have been able to apply the teachings of McGuigan et al. 2 to the compounds of Skulnick. However, McGuigan et al. 2 discloses that the need for metabolic activation by phosphorylation is common to nucleoside analogs in general (pp. 312-313, first paragraph) and that this approach has been taken with several different nucleoside analogs including AZT, araC, and araA. Thus one of ordinary skill in the art would be motivated to apply to nucleoside analogs in general and not merely to AZT and closely related compounds. This is especially true given that Skulnick already teaches 5'- phosphate compounds that would clearly be expected to suffer from the same problems with membrane permeability as AZT. Furthermore given that these phosphates would be expected to suffer from poor membrane permeability, one of ordinary skill in the art would expect that the modifications described by McGuigan et al. 2 would improve their membrane permeability and thus improve their activity. This effect would be expected to apply to both AZT phosphate and the phosphates of Skulnick because it relies on changes in the physical characteristics (charge and lipophilicity) of the compounds, which are relatively predictable.

Therefore the rejection is maintained and made **FINAL**.

Conclusion

Claims 1 and 8-15 are rejected. Claim 29 is objected to for depending from a rejected base claim but would be allowable if rewritten in independent form incorporating all the limitations of the rejected base claim and any intervening claims. Applicant's amendment necessitated the new ground(s) of rejection presented in this

Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERIC S. OLSON whose telephone number is (571)272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/
Examiner, Art Unit 1623
6/2/2009

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623